In This Issue

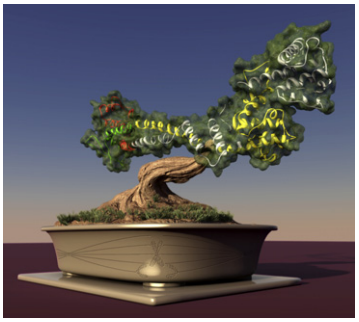
Cell

TIPE2 Reigns in Innate and Adaptive Immunity

PAGE 415

Immune homeostasis is essential for the normal functioning of the immune system and its breakdown leads to inflammatory disease. Sun et al. now report the identification of TIPE2, a new member of the tumor necrosis factor-α-induced protein-8 family (TIPE), which is required for immune homeostasis. TIPE2 deletion in mice leads to multiorgan inflammation and premature death. TIPE2-deficient cells are hyperresponsive to both Toll-like receptor and T cell receptor activation. Mechanistically, TIPE2 binds to caspase-8 and inhibits activating protein-1 and nuclear factor-κB activation while promoting Fas-induced apoptosis. TIPE2 is thus a negative regulator of innate and adaptive immunity with a critical role in immune homeostasis.

How Ndc80 Gets a Grip on Microtubuli



PAGE 427

Kinetochores are proteinaceous assemblies that mediate the interaction of chromosomes with the mitotic spindle. The Ndc80 complex is a direct point of contact between kinetochores and microtubules. Ciferri et al. provide insight into the molecular architecture of the Ndc80 complex and its mode of binding to microtubules by crystallizing an engineered Ndc80 complex. The structure reveals a microtubule-binding interface containing a pair of tightly interacting calponin-homology domains with a previously unknown arrangement. The interaction with microtubules is cooperative and is regulated by the Aurora B kinase. These results have implications for current models of kinetochore-microtubule attachment and centromere organization.

A Worthwhile Delay in Translation

PAGE 440

The signal recognition particle (SRP) is essential for targeting nascent chains to the endoplasmic reticulum (ER) and has been observed to exhibit an "elongation arrest" function in many systems. Now Lakkaraju et al. determine the significance of this arrest and demonstrate that efficient protein translocation into the ER is incompatible with normal cellular translation rates due to rate-limiting concentrations of SRP receptor. The absence of the SRP elongation arrest activity causes severe translocation defects with profound consequences on cell growth. The detrimental effects were reversed by either reducing the protein synthesis rate or by increasing SRP receptor expression. SRP therefore ensures that nascent chains remain translocation competent during the targeting time window as dictated by SRP receptor levels.

CaMKII Kicks Its Ca^{2+} Habit

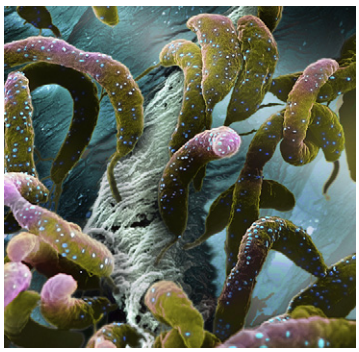
PAGE 462

Calcium/calmodulin-dependent kinase II (CaMKII) is a multifunctional enzyme that couples intracellular calcium levels to physiological and disease responses in many cell types. Mounting evidence has suggested that both CaMKII activation and localized oxidative stress play key roles in structural heart disease and arrhythmia. Erickson et al. now show that oxidation at a pair of methionine residues induces calcium-independent CaMKII activity that is reversed by methionine sulfoxide reductase A. Oxidation-dependent CaMKII activation is critical for angiotensin II-mediated and ischemic cell death in heart muscle. This redox mechanism for tuning CaMKII activity has broad implications for cardiomyocyte death and dysfunction.

Giving Feedback to Histidine Kinases

PAGE 452

Two-component signal transduction systems are ubiquitous in bacteria, lower eukaryotes, and plants controlling a wide range of cellular functions including cell differentiation, stress response, and virulence. Signal transduction from a sensor histidine kinase to a response regulator is generally believed to be a linear, unidirectional process. Paul et al. now demonstrate that a response regulator in the asymmetric bacterium *Caulobacter crescentus* can provide positive feedback and signal amplification by strongly stimulating its cognate sensor kinases. The findings indicate that such response regulators can facilitate crosstalk, feedback control, and long-range communication among members of the two-component phosphorylation network in a manner important for morphological development.



Regulating TRP with Pirt and PIP

PAGE 475

Many transient receptor potential (TRP) channels participate in sensory transduction by sensing various stimuli in the environment. PIP_2 is emerging as an important modulator of various ion channels including TRPs. Kim et al. now report the identification of a previously uncharacterized membrane protein, Pirt, which can bind TRPV1 (a molecular sensor of noxious heat and capsaicin) and PIP_2. Both behavioral and electrophysiological studies suggest that Pirt functions as a positive regulator of TRPV1. Importantly, Pirt and PIP_2 depend on each other to enhance TRPV1 current. Therefore, Pirt represents an important regulatory mechanism for TRPV1.

Endosomes, a New Signaling Router

PAGE 486

It has long been debated whether transmembrane receptors only initiate signaling from the plasma membrane or also, after internalization, from endosomes. However, the mechanisms and significance of endosomal signaling are poorly understood. Using mammalian cells and zebrafish as model organism, Schenck et al. now show that a central signaling hub, Protein Kinase B/Akt, signals from an endosomal compartment. This endosomal signaling, which crucially depends on the Rab5 effector APPL1, mediates substrate specificity among Akt targets and selectively controls cell survival. These results suggest that partitioning of Akt and selected effectors onto endosomal compartments represents a key mechanism contributing to the specificity of signal transduction in vertebrate development.

SIMU Puts Apoptotic Neurons to Rest

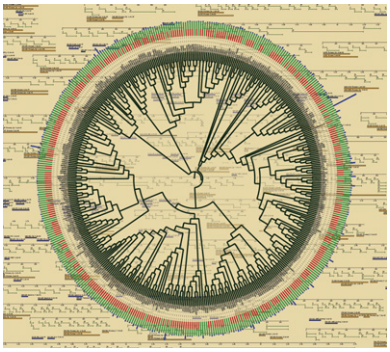
PAGE 498

The removal of apoptotic cells by phagocytic neighbors is essential for metazoan development but remains poorly characterized. Kurant et al. now identify a *Drosophila* phagocytosis receptor, six-microns-under (SIMU), which is required in phagocytic cell populations—including macrophages and glia—for the efficient clearance of apoptotic cells during development. As a member of an emerging family of phagocytosis factors that includes the CED-1 homolog Draper, SIMU acts upstream of Draper and affects the recognition and engulfment of apoptotic cells, while Draper mediates their subsequent degradation. The study also highlights the importance of glia as ''semiprofessional'' phagocytes in the nervous system.

Molecular Distinction among Astrocytic Masses

PAGE 510

Astrocytes are typically viewed as the central nervous system's cellular glue, functioning to hold together diverse neuronal subtypes. Now Hochstim et al. identify several positionally distinct subtypes of spinal cord astrocytes that can be distinguished by their expression of different axon guidance molecules. The positional identity of these astrocytes is specified by a combinatorial homeodomain transcriptional code, like that used to specify neuronal subtypes earlier in development. Thus, astrocytes are more diverse than previously suspected, opening up for future study the role of this diversity in brain development and function.



Cloning the Kinome

PAGE 537

Although the human genome has been sequenced, research into the mechanism of action of genes has been hampered by the fact that most human genes have not been isolated. This is true for even the most common class of cancer-associated genes, the protein kinases, which mediate the majority of signaling events in cells by phosphorylating and modulating the activity of other proteins. Varjosalo et al. now report the molecular cloning of >93% of full-length human protein kinase genes and generation of a corresponding collection of catalytically inactive kinases. Using this resource, the authors identify and characterize two novel kinases regulating the Hedgehog signaling pathway, which is associated with developmental disorders and cancer.

Mapping the *Arabidopsis* Epigenome Base by Base

PAGE 523

The state of chromatin modifications, such as DNA methylation and histone modification, has been referred to as the epigenome. By regulating the transcriptional potential of the genome, the epigenome plays a pivotal role in cellular differentiation, organogenesis, tissue formation, and aging. Therefore, a comprehensive view of the epigenome will greatly improve our understanding of development and disease processes. Lister et al. have developed high-throughput technologies for mapping the state of cytosine methylation and measuring the corresponding changes in mRNA and small RNA expression throughout the genome at single base resolution, allowing the first detailed view of the epigenome of the model plant *Arabidopsis thaliana*.